Claims 1-5 were pending at the time of the Final Action. Applicants submitted a response to the Final Action cancelling claims 3 and 4 and amending claims 1 and 5. An Advisory Action was mailed on May 21, 2002, indicating that the amendments would not be entered because they were considered to raise new issues requiring further search and to raise the issue of new matter. The Examiner's comments in the Advisory Action are also addressed herein.

Claims 3 and 4 are cancelled herein. Claims 1 and 5 are amended herein to clarify the subject matter of the claims. Support for the amendments to claims 1 and 5 can be found in the specification at page 2, lines 14-19. No claims are added herein. Thus, claims 1, 2 and 5 are currently pending. As required in 37 C.F.R. § 1.121(c)(1)(ii), a marked up version of the amendments to the specification and claims is attached hereto as Appendix A. For the Examiner's convenience, a clean copy of all pending claims is attached hereto as Appendix B.

B. The Amendments Do Not Introduce New Matter

The Advisory Action states that the amendments submitted in response to the Final Office Action would not be entered because they would require a new search and because they present new matter. Applicants respectfully traverse.

The amendments to claims 1 and 5 set forth the method in the form suggested by the Action mailed January 25, 2002. That is, they provide "1) a preamble, 2) method steps that clearly define what is to be done in each step, and 3) a conclusion that what was stated in the preamble was achieved." (Action ¶ 4, p. 5) Support for these amendments can be found in the

specification at page 2, lines 14-19. The amendments also "refer to GR gene and GRβ by SEQ ID NO: identifier," as suggested in the Action mailed October 13, 2000 (see p. 3).

Applicants submitted a sequence listing with their Response to Final Office Action, mailed April 25, 2002. This was required because the application "contain[s] disclosures of nucleotide and/or amino acid sequences." 37 C.F.R. § 1.821(b). For consistency and clarity, Applicants also amended the specification to refer to the SEQ ID NO:s presented in the sequence listing. This did not introduce new matter into the application because the sequences are disclosed in references cited in the application and incorporated by reference.

According to the MANUAL OF PATENT EXAMINING PROCEDURE (MPEP), it is proper for an applicant to incorporate the content of another document into the specification by reference to the document in the text of the specification. The MPEP explains that "[t]he information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed." MPEP § 2163.07. The MPEP instructs that when the material incorporated by reference is added into the specification, it is not new matter. *Id.*

The specification incorporates by reference Bamberger *et al.*, *The Journal of Clinical Investigation*, Glucocorticoid Receptor β, a Potential Endogenous Inhibitor of Glucocorticoid Action in Humans," 95:2435-2441 (1995) and Oakley *et al.*, *The Journal of Biological Chemistry*, "The Human Glucocorticoid Receptor β Isoform," 271(16):9550-9559 (1996), both of which discuss the GR gene and GRβ in detail. Both articles also refer to the characterization of the GRβ gene in Hollenberg *et al.*, *Nature*, "Primary structure and expression of a functional

human glucocorticoid receptor cDNA," 318(6047):635-641 (1985). The sequences of the genes (GR and GRβ) are also set forth at Genbank Accession No.s X03348 and M10901. Thus, these genes have been known since at least 1985 (see Hollenberg *et al.* supra).

C. Enablement Rejections

The outstanding Action in the parent case rejects all pending claims as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. In particular, the Action asserts that the recitations "aberrant alternate splice form of human glucocorticoid receptor (GRβ)", "genetic changes", "altered GRβ expression" and "changes outside" are unclear. The Action further asserts that claim 2 is indefinite for containing an improper Markush grouping and that claims 1-5 are indefinite for omitting essential elements. Applicants respectfully traverse.

It is apparent that the Advisory Action did not consider Applicants' arguments relating to the definiteness of the claims. Therefore, Applicants arguments are repeated here for the Examiner's convenience and consideration. If the following arguments are not found persuasive, it is requested that the Examiner provide a detailed reasoned explanation.

1. The Claim Terms Are Definite

The Action appears to take the position that at least the indefiniteness of the phrases "aberrant alternative splice form" and "altered GRβ expression" stems from the lack of a sequence listing providing the normal sequences of the gene and protein. Applicants note that nucleotide and amino acid sequences for GRβ (SEQ ID NO:1 and SEQ ID NO:2, respectively) and for GRα (SEQ ID NO:3 and SEQ ID NO:4, respectively) have been provided in a sequence

listing submitted herewith. Furthermore, references to SEQ ID NOs have been inserted in the specification and claims. It is believed that these amendments fully address the Action's concerns with respect to the indefiniteness at least of the phrases "aberrant alternative splice form" and "altered GRβ expression". Furthermore, it is submitted that the insertion of SEQ ID NOs, as suggested by the Examiner, does not change the scope of the claims whatsoever. Thus, it is believed that according to the Federal Circuit's recent opinion in *Bose v. JBL*, 61 U.S.P.Q.2d 1216 (Fed. Cir. 2001), Applicants have not surrendered any rights to equivalents of the claimed subject matter.

With respect to the phrases "genetic changes" and "changes outside", Applicants maintain that the meaning of these phrases is well known to the skilled artisan. Nevertheless, simply to progress the case to allowance, claims 3 and 4 have been cancelled herein. Thus, the rejection based on the indefiniteness of the phrases "genetic changes" and "changes outside" is moot.

2. ***Claim 2 Contains a Proper Markush Group***

The Action asserts that claim 2 is indefinite for containing an improper Markush grouping. According to the Action, the Markush group recited in claim 2 includes both methods and non-methods. Without further explanation or reasoning, the Action states that "denaturing gradient gel and single-stranded conformation polymorphism (SSCP) are not methods." Applicants respectfully disagree.

There are a number of techniques commonly used to detect variations in DNA sequences, and these are often used to screen for possible gene mutations. These techniques are well known by those skilled in the art (for example see Birren *et al.*, 1998; pp287-384 and Strachan & Read,

1996; pp. 367-399). Among the electrophoretic mobility alteration methods described in Birren (*see* Table 1, p. 289; attached hereto as Exhibit A) are: single-strand confirmation polymorphism (SSCP), denaturing gradient gel electrophoresis (DGGE), restriction enzyme fingerprinting, chemical cleavage of mismatches (CCM), constant denaturant gel electrophoresis (CDGE), and nondenaturing gel mismatch detection.

In SSCP, specific regions of normal and disease genes are amplified by PCR and loaded onto nondenaturing polyacrylamide gels. Single stranded DNA folds upon itself, and its electrophoretic migration is based on its sequence and length. Changes in DNA sequence are often identified by alterations in the DNA fragment mobility. DNA sequencing of fragments with altered mobilities identifies specific nucleotide changes.

In DGGE, DNA duplexes migrate through an electrophoretic gel with a gradient of denaturant (chemical or temperature). Migration of the DNA duplex the gel continues until the two strands dissociate, and further migration of this denatured DNA is inhibited. Thus, clearly both SSCP and DGGE are methods, known by those skilled in the art, that can detect a single nucleotide change through altered gel electrophoretic mobility.

3. The Claims Are Complete

The Action further asserts that all pending claims are incomplete for omitting essential elements. The Action suggests that an acceptable method claim contains three sections: 1) a preamble, 2) method steps that clearly define what is to be done in each step, and 3) a conclusion that what was stated in the preamble was achieved. The Action seems to imply that Applicants are required to explain how to accomplish the detecting and how to measure the defect.

In light of the Examiner's suggestion to format the claims into three sections, Applicants have amended the claims to put them into a more readable format. Thus, claims 1 and 5 now include the following three sections suggested by the Examiner: 1) a preamble, 2) method steps that clearly define what is to be done in each step, and 3) a conclusion that what was stated in the preamble was achieved. It is believed that all sections were inherently present in the claims as filed so that the amendments do not narrow the intended scope of the claims under *Bose*. Applicants have not included a detailed explanation as to how the detecting is done or how the defect is to be measured because it is believed to be unnecessary.

It is not the role of the claims to provide a self-contained explanation of every step. *S3 Inc. v. nVIDIA Corp.*, 59 U.S.P.Q.2d 1745 (Fed. Cir. 2001). The Federal Circuit recently explained that the purpose of the claims is simply to state the legal boundaries of the patented invention. The fact that some terms in the claim are hard to understand when viewed without benefit of the specification does not necessarily render the claim indefinite. *S3 Inc.*, 59 U.S.P.Q.2d at 1748. If the claims contain a term or terms that would be readily recognized and understood by persons skilled in the art, they satisfy the requirements for definiteness.

In *S3*, nVIDIA argued that the term "selector" as used in the application was indefinite because the electronic structure of the selector and the details of its electronic operation were not described in the specification. S3 provided evidence that a selector is a standard electronic component whose structure is well known in the relevant art. *Id.* at 1749. The Federal Circuit stated that "patent documents need not include subject matter that is known in the field of the invention and is in the prior art, for patents are written for persons experienced in the field of the

invention." *Id.* (citing *Vivid Technologies, Inc. v. American Science and Engineering, Inc.*, 200 F.3d 795, 804, 53 U.S.P.Q.2d 1289, 1295 (Fed. Cir. 1999)).

Likewise, in the present invention, it is submitted that the term "detecting" as used in the claims and specification would be readily understood by the skilled artisan and that techniques for accomplishing the detecting step are well known to the skilled artisan so that he would immediately understand the metes and bounds of the claim. Thus, it is believed that steps "disclosing how the 'detecting' is done" or "how the defect is measured" are unnecessary in light of well settled patent law.

In light of the foregoing arguments, Applicants respectfully request that the indefiniteness rejections be withdrawn.

D. The Claims Are Enabled

The outstanding Final Action next rejects claims 1-5 under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable the skilled artisan to make and/or use the invention. Much of the Action's reasoning appears to be very similar to the indefiniteness rejection addressed in Section B.3. above. That is, the Action takes the position that the specification lacks written description for how to use the assays listed to diagnose glaucoma, how to detect genetic changes in the GR gene leading to altered GR gene GRβ expression, how to determine if an agent that interacts with GRβ is useful for treating glaucoma, what defects in the GR gene are indicative of the presence of glaucoma, what genetic changes in or outside the GR gene lead to altered GRβ expression and how these changes are indicative of the presence of glaucoma, and how an agent that interacts

with GRβ or alters its expression is indicative of the presence of glaucoma. The Action further states that the specification and prior art lack experimental detail or data to support the statement in the specification that elevated intraocular pressure associated with POAG may be due to the aberrant expression of GRβ in the trabecular meshwork. The specification is also said to lack an explanation of the mechanism of GRβ interaction with GRα, how this relates to their interaction with glucocorticoids and their involvement with the onset of glaucoma. For these reasons, the claims are said to lack enablement within the meaning of the statute. Applicants respectfully traverse.

Applicants reiterate that a patent need not disclose what is well known in the art. *In re Wands*, 858 F.2d 731, 735, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). In fact, it is preferable that what is well known in the art be omitted from the disclosure. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986) (citing *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984)). In this case, the artisan skilled in the field of diagnosis of diseases using genetic information would be well aware of the techniques for detection of genetic changes and defects and would understand the phrases "genetic changes in the GR gene", "genetic changes outside the GR gene" and "altered GRβ expression." Moreover, the skilled artisan would be able to make the connection between such altered expression in the trabecular meshwork and a diagnosis of glaucoma.

The specification explains that it was the present inventors who discovered that the trabecular meshwork (TM) of glaucoma patients expresses both GRβ and GRα whereas the TM

resses only GRα. Spec. page 2, lines 9-12. Thus, the skilled
le that detection of GRβ in the TM of a patient reveals the
on seems to imply that since the prior art doesn't provide any
iscovery that glaucomatous TM cells express GRβ while non-
then the invention is not enabled. This reasoning fails to
-enablement.

v that the first paragraph of § 112 requires nothing more than
occhi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).
e provided through broad terminology or illustrative examples.
den, in rejecting a claim under the enablement requirement of
explanation as to why it believes that the scope of protection
quately enabled by the description of the invention provided in
." *Wright*, 999 F.2d at 1561-62 (citing *Marzocchi*, 439 F.2d at
The Action essentially attempts to punish Applicants for being
l expression of GRβ in glaucomatous TM cells and for filing a
eir discovery before anyone else reported the finding in the

ewith as Exhibit B copies of pages from a laboratory notebook
Wordinger, documenting the discovery of the differential
us TM cells. The dates on the laboratory notebook pages are
erein that the experiments were performed prior to the earliest

priority date of the application, December 5, 1996. Page one of Exhibit B illustrates that glucocorticoid receptor primers recognize GRα and GRβ. Page two of Exhibit B illustrates that GRβ is only expressed in glaucomatous trabecular meshwork (GTM) samples (lanes 5, 6, 7) and that it is not induced by dexamethasone (DEX) (lanes 9 and 11). Page three of Exhibit B illustrates that GRβ is expressed in two GTM cell lines and in one non-glaucomatous trabecular meshwork (NTM) sample. However, the occurrence of GRβ in the one NTM sample was only observed in one NTM cell line on one gel and the results were not repeatable. Page four of Exhibit B illustrates that GRβ was expressed in two GTM cell lines. No bands were observed in normal cell lines or in one GTM cell line.

The Action further asserts that a lack of description of the mechanism of GRβ interaction with GRα, how it relates to their interaction with glucocorticoids and their involvement with the onset of glaucoma must lead to a conclusion of non-enablement. The Action seems to take the position that the specification does not describe how to use the invention within the meaning of § 112, first paragraph because it does not describe how it works. Applicants submit that this is an improper basis for a rejection based on a failure to satisfy the how to use requirement of § 112, first paragraph. Generally, evidence of a biological or pharmacological activity of a compound, such as a gene sequence or protein, will be relevant to an asserted use, such as diagnosis of a disease, if there is a reasonable correlation between the activity in question and the asserted utility. *See* MPEP § 2107.03(I), p. 2100-43 (August 2001) (citing *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985); *In re Jolles*, 628 F.2d 1322, 206 U.S.P.Q. 885 (CCPA 1980); *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. 881 (CCPA 1980)). This

reasonable correlation may be presented as statistically relevant data establishing the activity of the compound, arguments or reasoning, publications, or any combination of these. The MPEP explains that "the applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use." MPEP at 2100-43 (citing *Nelson*, 626 F.2d at 857, 206 U.S.P.Q. at 884).

Applicants have shown that GRβ is expressed in glaucomatous TM cells and that it is not expressed in non-glaucomatous TM cells. One of skill in the art would reasonably conclude that the presence (activity) of GRβ in a sample containing TM cells from a patient indicates a glaucomatous condition. The Action provides no evidence that this conclusion is unreasonable. Therefore, it is believed that the claims are adequately enabled.

In light of the foregoing arguments, Applicants respectfully request that the rejection based on lack of enablement be withdrawn.

E. Conclusion

This is submitted to be a complete response to the Final Office Action outstanding in the parent case. It is respectfully submitted that Applicants' remarks herein adequately address the Examiner's concerns set forth in the Final Office Action. Thus, it is believed that the claims are now in condition for allowance. A notice of allowability is therefore respectfully requested.

The Examiner is invited to contact the undersigned attorney at (817) 551-4321 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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